Hyperbaric Oxygen Therapy Facilitates Healing of Chronic Foot Ulcers in Patients With Diabetes

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OBJECTIVE — Chronic diabetic foot ulcers are a source of major concern for both patients and health care systems. The aim of this study was to evaluate the effect of hyperbaric oxygen therapy (HBOT) in the management of chronic diabetic foot ulcers.

RESEARCH DESIGN AND METHODS — The Hyperbaric Oxygen Therapy in Diabetics with Chronic Foot Ulcers (HODFU) study was a randomized, single-center, double-blinded, placebo-controlled clinical trial. The outcomes for the group receiving HBOT were compared with those of the group receiving treatment with hyperbaric air. Treatments were given in a multi-place hyperbaric chamber for 85-min daily (session duration 95 min), five days a week for eight weeks (40 treatment sessions). The study was performed in an ambulatory setting.

RESULTS — Ninety-four patients with Wagner grade 2, 3, or 4 ulcers, which had been present for >3 months, were studied. In the intention-to-treat analysis, complete healing of the index ulcer was achieved in 37 patients at 1-year of follow-up: 25/48 (52%) in the HBOT group and 12/42 (29%) in the placebo group ($P = 0.03$). In a sub-analysis of those patients completing >35 HBOT sessions, healing of the index ulcer occurred in 23/38 (61%) in the HBOT group and 10/37 (27%) in the placebo group ($P = 0.009$). The frequency of adverse events was low.

CONCLUSIONS — The HODFU study showed that adjunctive treatment with HBOT facilitates healing of chronic foot ulcers in selected patients with diabetes.

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Diabetic foot ulcers are a common and serious complication of diabetes (1,2). Treatment often requires long-term hospital admissions and frequent outpatient visits. Furthermore, loss of mobility poses a great burden on the patient and the health care system (3). At centers of excellence, 19–35% of ulcers are reported as nonhealing (4–6). Thus, despite improvements in healing diabetic foot ulcers, there is still a need for new treatment strategies and methods.

Systemic hyperbaric oxygen therapy (HBOT) has been proposed as a medical treatment for diabetic foot ulcers (7). HBOT has been demonstrated to have an antimicrobial effect and to increase oxygenation of hypoxic wound tissues (8–10). This enhances neutrophil killing ability, stimulates angiogenesis, and enhances fibroblast activity and collagen synthesis (9,11,12). Thus, theoretically, HBOT could improve the healing of ischemic foot ulcers in patients with diabetes. HBOT has been advocated and adopted by a number of centers even though the evidence of its effectiveness is limited (13–16). The first published double-blinded, randomized, controlled trial by Abidia et al. (17) in 2003 suggested the benefit of HBOT, but the study was small and included only patients with Wagner grade 1 and 2 ulcers. Therefore, the clinical utility of HBOT in treating diabetic foot ulcers was not established. The final conclusion of an analysis completed in 2004 by the Cochrane Collaboration found that further research was needed and the need for larger randomized placebo-controlled studies was highlighted (13).

The aim of the Hyperbaric Oxygen Treatment in Diabetic Patients with Chronic Foot Ulcers (HODFU) study was to evaluate if adjunctive treatment with HBOT, when compared with treatment with hyperbaric air (placebo), would have any therapeutic effect on chronic foot ulcers in patients with diabetes.

RESEARCH DESIGN AND METHODS

— This study was initiated, designed, and performed by the authors. A steering committee was in charge of organization, data handling, and general conduct of the study. A blinded clinical event committee evaluated and classified all reported events as well as clinical outcome. The protocol was approved by the ethics committee at the Lund University.

The HODFU study was a randomized, single-center, double-blinded, placebo-controlled clinical trial that evaluated the effect of HBOT on ulcer healing in patients with diabetes and chronic foot ulcers. The outcomes for the group receiving HBOT were compared with those of the group receiving treatment with hyperbaric air. The study design and rationale were reported in detail previously (18).

All patients had diabetes and at least one full-thickness wound below the ankle for >3 months. They were previously treated at a diabetes foot clinic for a period of no <2 months. All patients were assessed by a vascular surgeon at the time of inclusion and only patients with adequate distal perfusion or nonreconstructable peripheral vascular disease were included in the study. Patients having an acute foot infection were included when the acute phase was resolved. Oral or local antibiotic treatment did not exclude patients

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from study participation. Exclusion criteria for study participation were contraindications for hyperbaric treatment (severe obstructive pulmonary disease, malignancy, and untreated thyrotoxicosis), current drug or alcohol misuse, vascular surgery in the lower limbs within the last two months, participation in another study, or suspected poor compliance. All participants provided written informed consent.

Procedures

Patients were stratified based upon arterial toe blood pressure (≤35 mmHg vs. >35 mmHg) before being randomly assigned to either of the treatment arms. Randomization was done in blocks of 10 using sealed envelopes.

The study was performed in an ambulatory setting. Treatment sessions were given in a multi-place hyperbaric chamber five days per week for eight weeks (40 treatment sessions). The treatment period could be extended to 10 weeks, but the number of treatments was not allowed to exceed 40. An HBOT session included a period of compression in air for 5 min, followed by a treatment period at 2.5 atmospheres absolute (ATA) for 85 min, and then a decompression period of 5 min. Patients from both groups could be treated in the same session as study gases were administered by masks and air or 100% oxygen entered the chamber through separate double-blinded pipes (19). Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic, which included treatment of infection, revascularization, debridement, off-loading, and metabolic control according to high international standards (18). Investigators did not intervene in the daily routine clinical management of the patients. Outcomes were measured every first week during the treatment period (first 8–10 weeks) and then at three-month intervals. Ulcers were graded using the Wagner classification system and ulcer areas were measured using Visitrak Digital (Smith & Nephew, Hull, England) (20).

End points

The primary end point was healing of the index ulcer. The index ulcer was defined as the ulcer with the largest area and a duration of at least three months at the time of inclusion. An ulcer was considered healed when it was completely covered by epithelial regeneration and remained so until the next visit in the study. Wagner grade 4 ulcers were considered healed when the gangrene had separated and the ulcer below was completely covered by epithelial regeneration. If a patient died during the follow-up period, he/she was censored at the time of the death. If a major amputation (above ankle amputation) was required, the ulcer was considered not to have healed. Secondary end points reported in this paper are major amputations and death.

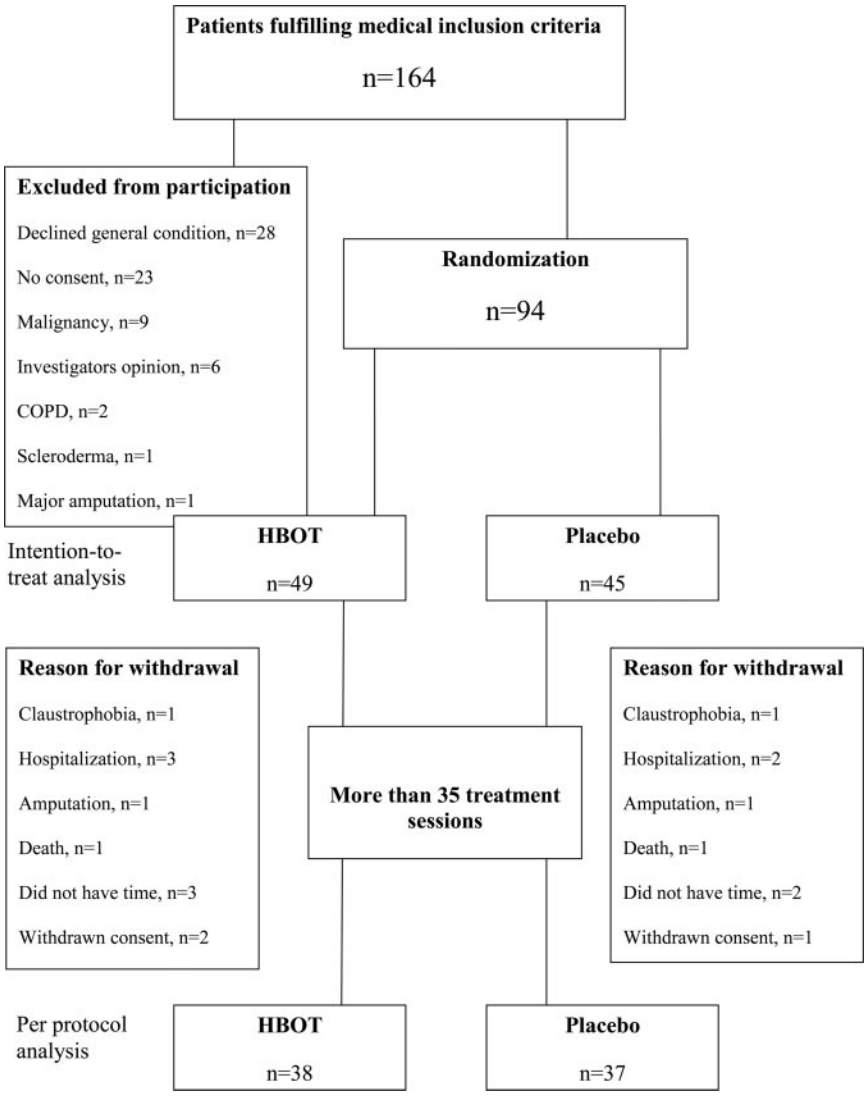

Figure 1—*Study flow chart of the HODFU study. COPD, chronic obstructive pulmonary disease.*

Statistical analysis

The treatment code was not broken until the last patient had completed the 1-year follow-up visit.

Statistical evaluation was initially performed as an intention-to-treat analysis. An analysis was also performed on those patients who received >35 treatments (per protocol analysis). Categorical variables were analyzed using contingency tables (Fisher exact test) and continuous variables using Mann-Whitney *U* test. A two-sided *P* value <0.05 was considered statistically significant. Statistical analysis was performed using Statistica software, version 8.0 (Statsoft, Tulsa, OK).

RESULTS

Enrollment and basal characteristics of the patients

During the inclusion period, a total of 164 eligible participants were registered: 23 (14%) did not consent to participation, 47 (29%) were excluded according to the study protocol, and 94 (57%) underwent randomization (Fig. 1).

The two groups had similar characteristics at baseline (Table 1). The median ulcer duration was 10 months and the

median ulcer area was 3 cm^2. A majority of index ulcers were classified as Wagner grade 3 and 4 (20). Vascular surgery was previously performed in the affected lower limb in 55% of the participants.

Treatment

Fifty-four (57%) patients completed all 40 treatment sessions, and 75 (80%) completed >35 sessions. Nine patients completed <10 treatment sessions, and the remaining 10 patients completed between 14 and 28 sessions. Early treatment termination was due to claustrophobia in two patients and worsening medical condition in nine patients (two deaths, two major amputations, and five hospitalizations). Eight patients decided to withdraw from the study.

Open vascular surgery in the affected lower limb was not performed on any study participant during the 1st year after inclusion, whereas percutaneous transluminal angioplasty (PTA) was carried out in 10 patients (Table 2).

Effect on ulcer healing

In the intention-to-treat analysis, complete healing of the index ulcer was achieved in 37 patients at 1-year of follow-up in 25/48 (52%) in the HBOT group and 12/42 (29%) in the placebo group ($P = 0.03$). In the per-protocol analysis, complete healing of the index ulcer occurred in 23/38 (61%) in the HBOT group and 10/37 (27%) in the placebo group ($P = 0.009$) (Fig. 2). The largest differences in healing rates between groups were seen at the nine-month follow-up. Numbers needed to treat to avert nonhealing of a chronic foot ulcer were 4.2 and 3.1 according to the intention-to-treat and per-protocol analysis, respectively. During the 1st-year of follow-up, new ulcers developed in nine patients in the HBOT group and eight patients in the control group.

Effects on amputation and death

Four participants—one in the HBOT group and three in the placebo group—died during their 1st year in the study. The patient in the HBOT group received eight treatments and died of multiple organ failure 20 days after inclusion. She was 87-years-old and had a medical history including severe peripheral artery disease, neuropathy, myocardial infarction, and heart failure. In the placebo group, the causes of death were myocardial infarction in two patients (at 162 days after 39 treatments and 218 days after 22

Table 1 —*Basal patient characteristics at randomization. Lower extremity data are given only for index ulcer limb. Categorical variables are given as percent and continuous variables as medians and ranges*

	HBOT	Placebo	
Number of patients	49	45	
Age (years)	69 (37–95)	68 (28–86)	n.s.
Females (%)	22	16	n.s.
Smoking habits	61	69	n.s.
Current (%)	22	29	n.s.
Previous (%)	41	38	n.s.
Pack-years (nonsmokers excluded)	26 (1–47)	25 (4–73)	n.s.
Mobility			
Walking without support (%)	43	44	n.s.
Walking with support (%)	38	31	n.s.
Wheelchair (%)	18	24	n.s.
Diabetes duration (years)	20 (1–63)	23 (3–54)	n.s.
Diabetes type 1/2 (%)	24/76	42/58	n.s.
Glycated hemoglobin (%)*	7.8 (4.2–11.0)	8.1 (5.0–12.5)	n.s.
Hemoglobin (g/l)	127 (95–156)	123 (95–160)	n.s.
Creatinine (μmol/l)	104 (52–804)	101 (48–687)	n.s.
C-reactive protein (mg/l)	8 (1–161)	7 (1–49)	n.s.
Leukocyte count (10^9/l)	8.5 (3.7–13.1)	7.7 (1.9–13.8)	n.s.
Concomitant diagnoses			
Hypertension (%)	76	73	n.s.
Hyperlipidemia (%)	88	87	n.s.
Myocardial infarction (%)	25	33	n.s.
Stroke (%)	16	16	n.s.
Congestive heart failure (%)	35	27	n.s.
Atrial fibrillation (%)	25	33	n.s.
Nephropathy (%)	90	80	n.s.
Dialysis (%)	6	7	n.s.
Renal transplant (%)	4	2	n.s.
Prior major amputation† (%)	14	7	n.s.
Prior minor amputation (%)	32	47	n.s.
Charcot foot (%)	4	9	n.s.
Medication			
Insulin (%)	90	91	n.s.
Metformin (%)	10	13	n.s.
Sulfonylurea (%)	12	16	n.s.
Statin (%)	69	60	n.s.
Aspirin (%)	63	56	n.s.
Clopidrogel (%)	8	13	n.s.
Warfarin (%)	18	24	n.s.
ACE-inhibitor or ARB‡ (%)	69	74	n.s.
β-blocker (%)	39	40	n.s.
Diuretics (%)	67	51	n.s.
Antibiotics, oral (%)	65	73	n.s.
Antibiotics, intravenous (%)	0	0	n.s.
Index ulcer size (cm^2)	3.1 (0.6–55)	2.8 (0.6–39)	n.s.
Ulcer duration (months)	9 (3–44)	10 (3–39)	n.s.
Wagner classification			
Grade 1 (%)	0	0	n.s.
Grade 2 (%)	24	27	n.s.
Grade 3 (%)	51	62	n.s.
Grade 4 (%)	24	11	n.s.
Grade 5 (%)	0	0	n.s.
Index ulcer location			
Toe (%)	35	47	n.s.

(continued)

Table 1—*Continued*

	HBOT	Placebo	
Plantar forefoot (%)	27	24	n.s.
Middle foot (%)	14	13	n.s.
Heel (%)	16	7	n.s.
Malleoli (%)	6	7	n.s.
Dorsal (%)	2	0	n.s.
Peripheral circulation			
Previous vascular surgery (%)	57	49	n.s.
Toe blood pressure (mmHg)	50 (5–130)	55 (15–160)	n.s.
Toe blood pressure ≤60 mmHg (%)	57	57	n.s.
Toe blood pressure ≤35 mmHg (%)	33	29	n.s.

*Glycated hemoglobin recalculated to % in Diabetes Control and Complications Trial standard, †above ankle amputation, ‡angiotensin II receptor blocker. n.s., not significant.

treatments) and sepsis derived from an infected foot ulcer in one patient (at 144 days after 40 treatments).

Three major amputations were performed in the HBOT group as compared with one in the placebo group within the 1st year. In the HBOT group, two of the three amputations were done within 2 months after inclusion and the third was done at 191 days. The amputation in the placebo group was performed 98 days after inclusion. All four patients had an arterial toe blood pressure ≤15 mmHg in the affected lower limb. Two of these ulcers were classified as Wagner grade 4 and two were classified as grade 3 ulcers (20). Four minor amputations were performed in each group during the 1st year of follow-up.

Adverse reactions

All together 3,225 treatment sessions were given in the HODFU study. As discussed above, one fatal outcome was seen in the HBOT group during the treatment period, and a relation between HBOT and this fatal outcome cannot be excluded. In the placebo group, one patient was hospitalized for 24 h after temporarily losing consciousness after a treatment session.

Hypoglycemia (symptoms and blood-glucose <3.0 mmol/l) within 6 h after treatment occurred in two and four patients in the HBOT and placebo groups, respectively (n.s.). One of the patients in the HBOT group was hospitalized due to the event.

One patient in the HBOT group endured barotraumatic otitis. Another four patients, two in each group, required myringotomy with tube placement due to pain caused by the inability to equilibrate air pressure through the eustachian tube.

In the HBOT group, treatment-related dizziness was seen in one patient and the worsening of cataracts in another. One case of minor head injury occurred in the placebo group after a fall inside the hyperbaric chamber. Oxygen toxicity, seizures, or pneumothorax were not seen.

CONCLUSIONS — The present study supports the concept that adjunctive treatment with HBOT enhances foot ulcer healing in selected patients with diabetes. Accordingly, in our patients with long-standing chronic ulcers at 1-year follow-up, HBOT doubled the number of healed ulcers as compared with adjunctive treatment with hyperbaric air used as placebo.

In this study, arterial toe blood pressure was not a discriminating factor for beneficial effect of HBOT (data not shown). Patients with arterial toe blood pressure as low as 5 mmHg did heal in the HBOT group, and we could not identify a lower level of arterial toe blood pressure for nonhealing. Ulcer healing rate in the placebo group might be lower than expected, probably mainly reflecting a long prestudy period of failure to heal.

Our findings are in agreement with those reported in previous randomized studies focused on ulcer healing by Abidia et al. (17), Duzgun et al. (21), Kessler et al.(22), and Kalani et al. (23). Abidia et al. evaluated the effect of HBOT compared with hyperbaric air in a double-blind study of ischemic Wagner grade 1 and 2 ulcers. In that study of 18 patients, a nonsignificant improvement of healing rate following HBOT was seen after six weeks, which reached statistical significance at 1-year follow-up. In the unblinded, ran-

Table 2 —*PTA was performed in 10 patients during the first year of follow-up. Baseline arterial toe blood pressure, number of treatment sessions given, and ulcer outcome are specified for those patients*

PTA intervention (months after randomization)	Total number of HBOT treatments	Arterial toe blood pressure at inclusion	Outcome of index ulcer	Amputation
HBOT Group				
3	40	15 mmHg	Unhealed	Above ankle amputation at 7 months
6	40	25 mmHg	Healed at 6 months	Toe amputation at 8 months
7	38	20 mmHg	Unhealed	Toe amputation at 10 months
7	40	30 mmHg	Healed at 3 months	No
7	38	40 mmHg	Healed at 12 months	No
8	40	20 mmHg	Unhealed	No
Placebo Group				
2	40	20 mmHg	Unhealed	No
3	37	45 mmHg	Unhealed	No
6	38	50 mmHg	Unhealed	No
7	38	25 mmHg	Healed at 9 months	No

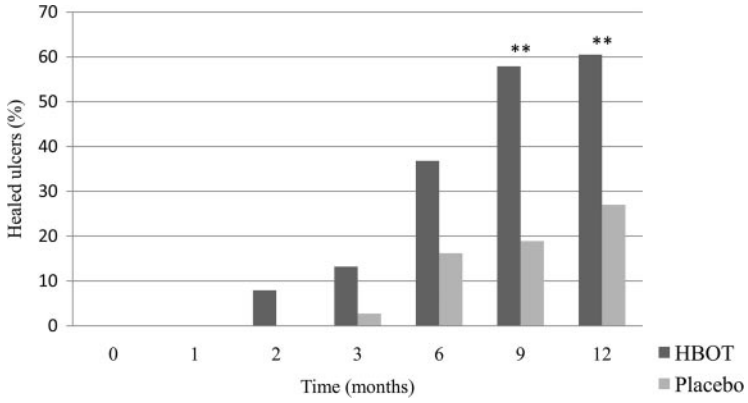

Figure 2—*Healing rates in patients given treatment with hyperbaric oxygen therapy (HBOT) as compared with hyperbaric air (placebo).* *P $<$ *0.05;* **P $<$ *0.01.*

domized study by Duzgun et al., the effect of HBOT was compared with standard therapy in 100 patients with a foot ulcer duration of at least four weeks. During a mean follow-up period of 92 weeks, primary healing was achieved in 66% of patients receiving HBOT compared with 0% following standard therapy (21). In the randomized trial by Kessler et al., the effect of two daily 90-min sessions of HBOT five days a week for two weeks was compared with regular treatment in 28 hospitalized patients with neuropathic Wagner grade 1 to 3 ulcers (22). After two weeks of treatment, the reduction in ulcer area was doubled in the HBOT group (P = 0.037). However, this improvement disappeared during the next two weeks of follow-up. The study by Kalani et al. included 38 patients with ischemic ulcers without full-thickness gangrene. After three years, 76% of the 17 patients receiving HBOT had healed their ulcers to intact skin compared with 48% of those given conventional treatment. However, these data should be interpreted with caution as the randomization procedure was not sustained through the study (23).

In contrast to our findings, some studies have shown the beneficial effect of HBOT in preventing amputations (8,21,23). Our study had insufficient power to analyze the rate of major amputations, which were only performed due to life-threatening infection and refractory pain. In the studies by Faglia et al. (8), Kalani et al. (23), and Duzgun et al. (21), amputation rates were substantially higher than in our study, suggesting these studies used other indications for major amputation (i.e., long-term unhealed ulcers) (8,21,23). This might indirectly be mirrored in toe blood pressure levels that were ≤15 mmHg in our amputated patients compared with 42 ± 30 mmHg in the study by Kalani et al. (23). Also, a possible bias effect cannot be excluded in open studies where the investigator may be involved in the decision to amputate.

Although >50% of our patients had had at least one previous vascular intervention at the time of randomization and the need for—or possibility of—vascular surgical intervention had been excluded at time of inclusion, PTA was performed in 10 patients (11%) within one year of randomization. This partly reflects a general problem in evaluating the effects of different treatment methods for diabetic foot ulcers and is not unique for our study. For instance in the study by Faglia et al. (8), vascular surgical intervention was performed in 38% of the patients during the follow-up period. The implications of these interventions on study outcome have been debated (24). In our study, however, PTA intervention cannot explain the higher ulcer healing rate in the HBOT group as only three ulcers, one of which was in the placebo group, healed following PTA.

The frequency (6%) of middle ear barotrauma or the need for myringotomy with tube placement was not higher in our study population of relatively old patients with severe cardiovascular disease and neuropathy compared with previously reported data in younger patients (25). In our treatment schedule, an HBOT session included a period of compression in air for 5 min, followed by a treatment period at 2.5 ATA for 85 min, and then a decompression period of 5 min. This schedule has been shown to be safe for scuba divers and our study showed it to be safe in our diabetic foot ulcer population where 3,225 treatments were given without decompression sickness, seizures, or pneumothorax.

In conclusion, the HODFU study, a double-blinded, randomized, placebo-controlled trial, showed that adjunctive treatment with HBOT facilitates healing of chronic foot ulcers in selected patients with diabetes.

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No potential conflicts of interest relevant to this article were reported.

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References

1. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, Edmonds M, Holstein P, Jirkovska A, Mauricio D, Ragnarson Tennvall G, Reike H, Spraul M, Uccioli L, Urbancic V, Van Acker K, van Baal J, van Merode F, Schaper N. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe: baseline results from the Eurodiale study. Diabetologia 2007;50:18–25
2. Boulton AJ. The diabetic foot: grand overview, epidemiology and pathogenesis. Diabete Metab Res Rev 2008;24(Suppl. 1):S3–S6
3. Ragnarson Tennvall G, Apelqvist J. Health-economic consequences of diabetic foot lesions. Clin Infect Dis 2004;39(Suppl. 2):S132–S139
4. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, Boulton AJ. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabet Med 2001; 18:133–138

5. Gershater MA, Löndahl M, Nyberg P, Larsson J, Thörne J, Eneroth M, Apelqvist J. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia 2009;52:398–407
6. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. Am J Surg 1998;176:5S–10S
7. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. J Postgrad Med 1992;38:112–114, 111
8. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. Diabetes Care 1996;19:1338–1343
9. Brown GL, Thomson PD, Mader JT, Hilton JG, Browne ME, Wells CH. Effects of hyperbaric oxygen upon S. aureus, Ps. aeruginosa and C. albicans. Aviat Space Environ Med 1979;50:717–720
10. Marx RE, Ehler WJ, Tayapongsak P, Pierce LW. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. Am J Surg 1990;160:519–524
11. Brismar K, Lind F, Kratz G. Dose-dependent hyperbaric oxygen stimulation of human fibroblast proliferation. Wound Repair Regen 1997;5:147–150
12. Reng JJ, Hussan MZ, Constant J, Hunt TK. Angiogenesis in wound healing. J Surg Pathol 1998;3:1–7
13. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2004;2:CD004123
14. Barnes RC. Point: hyperbaric oxygen is beneficial for diabetic foot wounds. Clin Infect Dis 2006;43:188–192
15. Berendt AR. Counterpoint: hyperbaric oxygen for diabetic foot wounds is not effective. Clin Infect Dis 2006;43:193–198
16. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. PM R 2009;1:471–489
17. Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, Masson EA, McCollum PT. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg 2003;25:513–518
18. Löndahl M, Katzman P, Nilsson A, Hammarlund C, Sellman A, Wykman A, Hugo-Persson M, Apelqvist J. A prospective study: hyperbaric oxygen therapy in diabetics with chronic foot ulcers. J Wound Care 2006;15:457–459
19. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plast Reconstr Surg 1994;93:829–833
20. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981;2:64–122
21. Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. J Foot Ankle Surg 2008;47:515–519
22. Kessler L, Bilbault P, Ortéga F, Grasso C, Passemard R, Stephan D, Pinget M, Schneider F. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care 2003;26:2378–2382
23. Kalani M, Jörneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers: long-term follow-up. J Diabetes Complications 2002;16:153–158
24. Hinchliffe RJ, Valk GD, Apelqvist J, Armstrong DG, Bakker K, Game FL, Hartemann-Heurtier A, Londahl M, Price PE, van Houtum WH, Jeffcoate WJ. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabete Metab Res Rev 2008;24(Suppl. 1):S119–S144
25. Plafki C, Peters P, Almeling M, Welslau W, Busch R. Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med 2000;71:119–124